Part I Overview Information

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH), (http://www.nih.gov)

Components of Participating Organizations

This Program Announcement (PAR) is developed as an NIH roadmap initiative (http://nihroadmap.nih.gov). All NIH Institutes and Centers participate in roadmap initiatives. The PAR will be administered by the National Institute of Mental Health (NIMH) on behalf of the NIH.

Title: Solicitation of Assays for High Throughput Screening (HTS) in the Molecular Libraries Screening Centers Network (MLSCN)

Announcement Type
New

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Council Review Date(s): Not applicable
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Due Dates for E.O. 12372
Not Applicable

Additional Overview Content

Executive Summary

The Molecular Libraries Screening Centers Network (MLSCN), a component of NIH Roadmap, will be a national resource capable of providing automated high throughput screening (HTS) facilities, diverse compound libraries, and HTS for the identification of small molecules (compounds) that are active in diverse biological assays, as well as synthetic chemistry to improve the biological utility of these molecules as bioactive probes for in vitro, and potentially in vivo, studies of normal and abnormal physiology of cells, organs, model systems, and/or organisms. Compound structures, screening data, and assay protocols generated by the MLSCN will be placed into a recently established public database (PubChem). Information about MLSCN compounds will be made available to all researchers, who will be free to adopt them in biological and biomedical research studies.

The ultimate goal of the MLSCN is to use as screens a variety of innovative biological, biophysical and cell-based assays for biological targets or processes for which there are limited selective and potent small molecule modulators available to the public. Through this Program Announcement (PAR), the MLSCN is soliciting applications from investigators who have developed innovative assays and are interested in having their assay(s) used in the MLSCN to screen a large number of compounds maintained in a central Small Molecule Repository, and furthermore, interested in expanding the utility of their assay(s) for producing useful *in vitro* and/or *in vivo* chemical probes.

- The purpose of this Program Announcement (PAR) is to invite investigators to seek access for their HTS assays to the Molecular Libraries Screening Centers Network (MLSCN). The MLSCN intends to screen 100-200 HTS assays per year to fully utilize the capacity of screening centers.
- Although the primary function of this process is to select assays for implementation in the MLSCN, the mechanism to be used for application, review, and selection will be the Small Research Grant R03 award in a form that provides limited funding for 1year.
- Up to $3000 will be available for each award to cover assay implementation costs for applicant investigators, including providing required reagents and travel to the screening centers.
- The total number of awards to be made depends on the scientific merit of applications and the funds available.
- Eligible organizations include for-profit or non-profit, public or private, and domestic or foreign institutions and organizations, as well as governmental units and agencies.
- Eligible principal investigators include any individual with the skills, knowledge and resources necessary to carry out the proposed research.
- There is no limit to the number of scientifically different applications an applicant may submit under this announcement but each application must propose a different HTS assay.
- Applications must be prepared using the PHS 398 application forms which can be downloaded at http://grants.nih.gov/grants/funding/phs398/phs398.html
- Telecommunications for the hearing impaired is available at: TTY 301-451-0088

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

Background

The National Institutes of Health (NIH) is committed to a major effort to broaden access to high-throughput screening (HTS) technologies, and the information produced by these approaches, for researchers in academia, government, and non-profit institutions. The public sector has not yet taken advantage of the considerable potential of HTS to advance the understanding of biology and disease mechanisms because access by academic scientists to automated screening facilities and diverse compound libraries is very limited. The Molecular Libraries Roadmap Initiative (http://nihroadmap.nih.gov/molecularlibraries/index.asp) will establish such resources and to facilitate the broad application of HTS in biomedical research in the public sector. The NIH wishes to enhance access to HTS capabilities for the academic community in order to speed the discovery of molecular research tools (e.g., ligands, imaging probes, and new activities of existing drugs) that will be available to the public sector. The Molecular Libraries effort should also catalyze scientific breakthroughs that will contribute to the identification of molecular entities or molecular classes that may accelerate the development of therapeutics by the private sector. Through this approach, NIH wishes to stimulate research in the following areas: 1) discovery of novel biological targets that can elucidate studies of cell function and disease mechanisms; 2) development, validation, and application of screening assays and disease models to evaluate the activity of novel small molecules; and 3) use of chemical genomic approaches to characterize the biology of genes of interest, cellular processes, and proteins associated with disease processes.

The Molecular Libraries Screening Centers Network (MLSCN): (http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-017.html), which will be established in 2005, will consist of 6 or more screening centers and will be capable of implementing innovative HTS approaches to identify compounds that are active in target-based and phenotypic assays. Each screening center will conduct 10-20 HTS assays annually using 96-well, 384-well or 1536-well plate formats, as appropriate to the specific assay and screening platform. The MLSCN will use a variety of biological assays solicited from the scientific community. The MLSCN, as a national research resource, will interface with other components of the Molecular Libraries Roadmap initiative, including the Small Molecule Repository, PubChem (http://pubchem.ncbi.nlm.nih.gov), and ongoing initiatives for cheminformatics and for technology development in the areas of assay development, chemical diversity, screening instrumentation, and algorithms for predicting biological activity of small molecules (see http://nihroadmap.nih.gov/molecularlibraries/grants.asp). The Small Molecule Repository will acquire and maintain a collection of up to 500,000 compounds, from both commercial and academic sources, with well-known or unknown biological activities and diverse chemical structures. The repository will distribute compounds to the screening centers for HTS. HTS hits, the active compounds identified through initial screening, will be developed within the MLSCN through optimization chemistry and further screening into useful bioactive probes that can be used by the scientific community to study molecular targets, cellular pathways, and potentially as starting points for drug development that will occur outside the MLSCN. The chemical structures of the compounds in the NIH repository, along with the related screening data, and assay protocols generated by the MLSCN will be deposited into a recently established public database PubChem. Information about the bioactive compounds will be made available to all researchers, who will be free to adopt them in biological and biomedical research studies. For related Molecular Libraries Roadmap assay development initiatives, see http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-011.html.

Objectives of the Project

The objective of this Program Announcement (PAR) is to invite HTS assay applications to support the Molecular Libraries Screening Centers Network (MLSCN). The goal of the MLSCN is to optimize and implement a variety of innovative biological, biophysical and cell-based assays for biological targets or processes for which there are limited selective and potent small molecule modulators available to the public. Applications are invited from investigators who have developed innovative assays for use both in basic research and in therapeutics development programs, and are interested in having them used within the MLSCN to screen the repository library. The MLSCN intends to select approximately 100-200 assays per year for implementation within the network of screening centers.

Services Provided by the MLSCN

The MLSCN will provide the following services for those assays accepted for this program.

1. Assay Implementation: The MLSCN will adapt, optimize and automate existing target-based and cell-based phenotypic assays obtained from the scientific community to 96-well, 384-well or 1536-well plate format as appropriate to the specific assay, screening approach, and level of throughput anticipated. The MLSCN will be capable of implementing assays using a variety of detection readouts such as absorbance, fluorescence, luminescence, scintillation proximity assay (SPA), fluorescence energy transfer (FRET), bioluminescence resonance energy transfer (BRET), biophysical readouts, and cell-based imaging screens.

2. Compound Library: The Small Molecule Repository is in the process of acquiring a collection of up to 500,000 compounds with known or unknown biological activities and diverse chemical structures, and it will maintain these compounds and distribute them to the MLSCN screening centers.

3. HTS Screening: The MLSCN will screen the repository compounds for biological activity in HTS assays to identify and confirm hits. Secondary assays, using a different readout, will be performed on initial hits in order to minimize false-positive results.

4. Optimization Chemistry: The MLSCN will provide a moderate level of optimization chemistry capabilities to provide analogues of initial hit compounds to improve properties such as potency and solubility. Chemistry efforts are expected to include designing initial structure-activity relationships (SAR) and generating analogues around a confirmed hit.

5. HTS Informatics: The MLSCN will provide informatics support to track compounds, assays, and screening data. The MLSCN will produce HTS reports that include the following information: 1) the nature of the modifications and tests performed on the assay, 2) the compounds screened with the assay, 3) the identities of active compounds and their effective concentrations, and 4) SAR analysis of active compounds. Any users of data deposited into PubChem will be required to acknowledge the source of the data. The PubChem and repository web sites will assist investigators in obtaining active compounds for their use in further research by identifying a source for purchase or synthesis of particular compounds.

Guidance for Assay Application

Since assays accepted by the MLSCN will be used in high-throughput, robotic testing of compounds from the repository, the assays submitted must have been developed sufficiently to be adaptable to HTS with only a modest effort. Nevertheless, it is anticipated that many assays will still need to undergo a certain amount of further development to be readily usable in HTS format; such development will be accomplished through the joint efforts of the submitter and the MLSCN selected to implement the assay. Assay applications will be evaluated in terms of the following characteristics:

1. Readiness for or adaptability to HTS: HTS assays are primarily characterized by miniaturization and automation, and are normally conducted in microtiter modes, such as 96-well, 384-well or 1536-well plates. Assays submitted for HTS should be easy to automate and steps such as centrifugation, filtration and extraction should be avoided. Homogeneous i.e. “mix and measure” assays are preferable.

2. Assay performance: Assays should be robust, reproducible and meet minimum statistical thresholds for robotic screening. The Z' parameter is commonly used to quantify assay performance, and it considers both the signal-to background and reproducibility of the assay. Assays with Z' parameters >0.5 are typically HTS-compatible. The coefficient of variation (CV) determined from the entire sample and control wells of the microtiter plate should not exceed 10%. Between-plates and day-to-day variations also provide useful information on how well the assay will perform.

3. Diversity of assays and targets: The following are some possible classes: 1) target-based biochemical assays may include enzymatic assays (such as those for kinases, proteases and transferases), and receptor-ligand binding assays (such as those for G-protein coupled receptors (GPCRs, including orphan GPCRs), ion channels, transporters, nuclear receptors, and new targets emerging from genetic and proteomic research in model systems and in human diseases); 2) cell-based assays could include functional assays, reporter gene assays and phenotypic assays for cellular processes and pathway analysis (e.g.,

viability assays for proliferation or apoptosis) or model organisms (e.g., yeast, C. elegans, zebrafish, etc); 3) assays for non-traditional targets of interest, including transcription factors, nucleic acids, multimeric proteins, membrane proteins, polymorphic gene products, subcellular processes such as molecular trafficking and translocation, post-transcriptional editing or splicing of gene products, and protein or RNA stabilization; and 4) other assays, including those for metabolism, bioavailability, toxicity, and blood-brain barrier permeability.

Material and Data Sharing

Submitting investigators will be required to provide necessary reagents, such as cells expressing recombinant enzymes/proteins, primary and secondary antibodies, tagged peptide substrates, and available positive controls (e.g., a known inhibitor of the target). Investigators are expected to adopt the uniform policies, such as data sharing, and procedures of the MLSCN. All screening data and descriptions/protocols for assays optimized for HTS by the MLSCN will be deposited in PubChem immediately after they have been certified for accuracy. All data generated by the MLSCN will be freely available to the research community in a form that will support redisplay and reanalysis, so that maximal utility of this research resource will be realized. See details of NIH data sharing guidance http://grants.nih.gov/grants/guide/notice-files/NOT-RM-04-014.html.

Project Oversight

As part of the larger Molecular Libraries Roadmap initiative, projects that are funded under this PAR are subject to oversight and evaluation of each aspect of the effort.

MLSCN ASSAY ACCESS COMMITTEE. This NIH committee will evaluate assay proposals for scientific merit and feasibility. The Scientific Review Administrator (SRA) for this panel will be an NIH review staff member, and the panel members will be primarily non-federal scientists. Recommendations of the MLSCN Assay Access Committee will be communicated to the NIH Project Team and to the MLSCN Steering Group.

MLSCN STEERING GROUP. The Steering Group for the overall MLSCN consists of the Director (PI) of each of the screening centers, as well as NIH Program Managers and Science Officers, and will be the primary operational governing board of the MLSCN. The functions of this group include: 1) recommending the assignment and scheduling of assays and tasks, 2) developing guidelines to standardize the validation of screening data in different types of assays across centers; and 3) developing uniform procedures and policies for assay validation, data quality measures, assessment procedures, and annotation conventions for data depositions in PubChem.

NIH PROJECT TEAM. The NIH Project Team will serve as the governing body that coordinates and oversees the interaction of NIH with the centers and the MLSCN Steering Group.

Section II. Award Information

1. Mechanism(s) of Support

This access and funding opportunity will use the NIH Small Research Grant (R03) award mechanism, designated for projects that can be carried out in a short period of time with limited resources (limited to 1 year, up to $3000 direct costs). Information on the R03 mechanism is available at http://grants.nih.gov/grants/funding/r03.htm and http://grants.nih.gov/grants/guide/pa-files/PA-03-108.html. A s an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This funding opportunity uses the just-in-time budget concepts. It also uses the non-modular budget format described in the PHS 398 application instructions (see http://grants.nih.gov/grants/funding/phs398/phs398.html). A detailed categorical budget for the "Initial Budget Period" and the "Entire Proposed Period of Support" is to be submitted with the application.

2. Funds Available

Through its funding of the MLSCN, NIH will support the costs of assay automation, screening and optimization chemistry (http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-017.html). Applications received in response to this Program Announcement (PAR) will compete for funds in the general funding pool of the participating NIH Roadmap. Up to $3,000 will be available for each award for investigators submitting the assays to travel to the screening centers and to provide necessary reagents for assay implementation. Other funds are available to support the Molecular Libraries Roadmap assay development initiatives (see http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-05-011.html).

The total amount awarded and the number of awards will depend on the number of applications received, their relative scientific merit, and the general availability of funds for NIH Roadmap. The earliest possible start date for applications submitted in response to this program announcement is August-September 2005.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- For-profit organizations
- Non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State government
- Units of local government
- Eligible agencies of the Federal government
- Foreign Institutions
- Domestic Institutions

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

2. Cost Sharing or Matching

Cost sharing is not required.

3. Other-Special Eligibility Criteria

There is no limit to the number of scientifically different applications an applicant may submit under this announcement, but each application must propose a different HTS assay.

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 398 application instructions are available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applicants must use the currently approved version of the PHS 398. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the most current PHS 398 research grant application instructions and forms. Applications must have a D&B Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at http://www.dnb.com/us/. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form and the YES box must be checked.

Additional Instructions: Use the PHS 398 form with the following modifications:

For R03 applications, follow instructions at http://grants.nih.gov/grants/guide/pa-files/PA-03-108.html. The following exceptions to the general R03 instructions will apply for this PAR:

Research Plan: Items a - d of the Research Plan (Specific Aims, Background and Significance, Preliminary Studies, and Research Design and Methods) should include the following sections:

- Rationale: biological significance and potential impact of the assay on the scientific field of study;
- Materials and Methods: include sources of specific materials, specify reagents, software, and instrumentation;
- Assay protocol: a detailed assay protocol for the primary and secondary assays;
- Results to date: assay performance and quality controls, responses to pharmacological standards or other control conditions, feasibility for miniaturization and automation for HTS, tolerance to the effect of DMSO, reagent stability, etc;
- Secondary confirmatory assay: provide an available secondary screening assay to confirm hits and eliminate false positives. This secondary assay should use a different readout than the primary assay.
- Cost estimation: estimate cost of reagents that are commercially available. These costs should be calculated for a single well of a 96-well plate assuming an assay volume of 200 ul.
- Future plans: describe future plans for the use of the hits in a follow-up research program, either biological research or therapeutics development.
- Material and data sharing: describe material(s) to be provided to the screening center; indicate if there are any issues associated with the assays or reagents which may impede their use within the MLSCN in achieving the goals of the MLSCN if the assay is selected for implementation.

Page limitation for Research Plan: 10 pages single-spaced (excluding appendices).

Appendix: Publications or other printed material should not be included in the appendix. The appendix may include original, glossy photographs or color images of data provided that a photocopy (may be reduced in size) is also included within the page limits of the research plan.

Up to two revisions of a previously reviewed application are allowed. For such amended applications, an additional 1 page is allowed for a response to the prior review. This Introduction should be inserted at the very beginning of the Research Plan.

3. Submission Dates and Times

Applications must be mailed on or before the receipt date described below (Section IV.3.A). Submission times N/A.

3.A. Receipt, Review and Anticipated Start Dates

Letter of Intent Receipt Date: March, 16, 2005; August 16, 2005; December 21, 2005; April 20, 2006
Application Receipt Date(s): April 13, 2005; September 14, 2005; January 18, 2006; May 18, 2006
Peer Review Date: July-August 2005; December 2005-January 2006; April-May, 2006; August-September, 2006
Council Review Date: Not applicable
Earliest Anticipated Start Date: August 2005

3.A.1. Letter of Intent

Prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this funding opportunity

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document.

The letter of intent should be sent to:

Ingrid Li, Ph.D.
Molecular Libraries Assay Access Team
NIH Molecular Libraries & Imaging Roadmap
National Institute of Mental Health/NIH/DHHS
6001 Executive Boulevard, Room 7185, MSC 9641
Bethesda, MD 20892-9641
Rockville, MD 20852-9641 (for express/courier service)
Telephone: (301) 443-5288
FAX: (301) 402-4740
Email: ili1@mail.nih.gov

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 398 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and three signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

At the time of submission, two additional copies of the application must be sent to:

Yong Yao, Ph.D.
NIH Molecular Libraries & Imaging Roadmap
Scientific Review Branch
National Institute of Mental Health/NIH/DHHS
6001 Executive Boulevard, Room 6149, MSC 9608
Bethesda, MD 20892-9608 (20852 for overnight couriers)
Telephone: (301) 496-9223
FAX: (301) 402-0182
Email: yyao@mail.nih.gov

3.C. Application Processing

Applications must be **received on or before the application receipt date(s)** described above (Section IV.3.A.). If an application is received after that date, it will be returned to the applicant without review. Upon receipt, applications will be evaluated for completeness by CSR and responsiveness by the NIMH.

The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The NIH will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within eight (8) weeks.

4. Intergovernmental Review

This initiative is not subject to intergovernmental review.

5. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm (see also Section VI.3. Reporting).

6. Other Submission Requirements

Plan for Sharing Research Data

Since the inception of the ML Roadmap, NIH has emphasized that in order to yield the maximum benefit, all physical and intellectual research resources should be publicly available. There are strong scientific arguments supporting this position. Small-molecule probes that selectively interact with biological targets are key research tools for understanding the functions of proteins and for elucidating biological pathways. A collection of such probes that would allow the comprehensive study of all of the proteins and other gene products encoded by the human genome would be an invaluable contribution to biomedical research. It will take the combined efforts of researchers in the public and private sectors many years of using small-molecule probes to completely characterize the biology of genes and proteins in health and disease, and then to use that information to develop approaches that will improve public health. Clearly, the open sharing of data, research tools, and resources will lead more rapidly to the identification and validation of novel targets for drug discovery, and will facilitate the rapid development of therapeutics by both the private and public sectors, with resulting benefits to public health, especially for rare or marginalized disorders.

All applicants must include a plan for sharing research data in their application. The NIH data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity should include a description of how final research data will be shared, or explain why data sharing is not possible.

The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score.

Sharing Research Resources

Guidance for Community Resources The following data and materials generated or developed through the ML Roadmap initiative are expected to be community resources: (1) primary data from HTS and from secondary screens; (2) protocols for assays implemented in the MLSCN; (3) the chemical structures of compounds tested in the MLSCN; and (4) the optimization chemistry protocols for probe development conducted within the MLSCN centers. In keeping with this approach, NIH expects that (1) all assays and assay protocols submitted to the NIH under this PAR and (2) biological screening data derived from implementing the assays in the MLSCN will be made readily available and accessible, consistent with other facets of the ML Roadmap http://grants.nih.gov/grants/guide/notice-files/NOT-RM-04-014.html.

It is NIH's understanding that the utility of the resources and data generated by the ML initiative will be maximized if they are treated as community resources and made broadly available, consistent with achieving the goals of the ML Roadmap. While NIH recognizes that under the Bayh-Dole Act, awardees have the right to elect title to subject inventions and seek appropriate IP protection, the data sharing and IP plans should take all of the above considerations into account. Applicants should provide clear explanations and rationales for their plans, especially for any proposed plan that involves principles differing from those described in this PAR.

A separate component of the IP plan should address any other data and resources that are expected to be generated by the grantees under this PAR. NIH encourages applicants to consider inclusion of "non-assert" language in IP plans for all potentially patentable inventions to ensure that, while an institution might apply for a patent on an invention, the institution would not attempt to enforce that patent against organizations utilizing the technology for research purposes.

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication (NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131). Investigators responding to this funding opportunity should include a plan for sharing research resources addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the resources sharing plan and any related data sharing plans will be considered by Program staff of the funding organization and by NIH Project Team staff when making recommendations about funding applications. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590, http://grants.nih.gov/grants/funding/2590/2590.htm). See Section VI.3. Reporting.

Submitting investigators will be required to provide necessary reagents such as cells expressing recombinant enzymes/proteins, primary and secondary antibodies, tagged peptide substrates, and available positive controls (e.g., a known inhibitor of the target).

Section V. Application Review Information

1. Criteria

The following will be considered in making funding decisions:

- Scientific merit of the proposed assay as determined by peer review
- Availability of funds
- Relevance of program priorities

2. Review and Selection Process

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIH Molecular Libraries Screening Centers Roadmap Project Team. Incomplete applications will not be reviewed.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NIMH in accordance with the review criteria stated below.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score.
- Receive a written critique

The goals of NIH supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field? Is this assay for a novel biological target or cellular process? Is there no known small molecule modulator for this biological target available? Is there an adequate plan for evaluating the activities of the compounds identified in a high throughput screen, e.g., in secondary screens? Are there important and well-defined goals for the use of active compounds identified with the proposed assay, either as research tools or for therapeutics development?

2. Approach. Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

2.A. Additional Review Criteria:

In addition to the above criteria, the following items will continue to be considered in the determination of scientific merit and the priority score:

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

2.B. Additional Review Considerations

Budget: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

2.C. Sharing Research Data

Data Sharing Plan: The reasonableness of the data sharing plan or the rationale for not sharing research data may be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score. The funding organization will be responsible for monitoring the data sharing policy. The presence of a data sharing plan will be part of the terms and conditions of the award. Program staff of the funding organization and NIH Project Team staff will be responsible for monitoring the data sharing policy. http://grants.nih.gov/grants/policy/data_sharing.

2.D. Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication (See the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps/part_ii_5.htm#availofrr and http://ott.od.nih.gov/newpages/rtguide_final.html). Investigators responding to this funding opportunity should include a sharing research resources plan addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the resources sharing plan will be considered by Program staff of the funding organization when making recommendations about funding applications. Program staff may negotiate modifications of the data and resource sharing plans with the awardee before recommending funding of an application. The final version of the data and resource sharing plans negotiated by both will become a condition of the award of the grant. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590). See Section VI.3. Reporting.

3. Anticipated Announcement and Award Dates

Not applicable

Section VI. Award Administration Information

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1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a Summary Statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm).

A formal notification in the form of a Notice of Grant Award (NGA) will be provided to the applicant organization. The NGA signed by the grants management officer is the authorizing document.

For current NIH grantees, the NGA will be sent via email to the administrative official whose name is listed in Block 12 on the Face Page of the Form PHS 398, for new awardees the NGA will be sent via postal mail.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs. See Also Section IV.5. Funding Restrictions.

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm) and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm).

2.A. Cooperative Agreement Terms and Conditions of Award

Not applicable

3. Reporting

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually (http://grants.nih.gov/grants/funding/2590/2590.htm) and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific / Research Contacts:

Ingrid Li, Ph.D.
Molecular Libraries Assay Access Team
National Institute of Mental Health/NIH/DHHS
6001 Executive Boulevard, Room 7185, MSC 9641
Bethesda, MD 20892-9641
Rockville, MD 20852-9641 (for express/courier service)
Telephone: (301) 443-5288
FAX: (301) 402-4740
Email: ili1@mail.nih.gov

2. Peer Review Contacts:

Yong Yao, Ph.D.
NIH Molecular Libraries & Imaging Roadmap
Scientific Review Branch
National Institute of Mental Health/NIH/DHHS
6001 Executive Boulevard, Room 6149, MSC 9608
Bethesda, MD 20892-9608 (20852 for overnight couriers)
Telephone: (301) 496-9223
FAX: (301) 402-0182
Email: yyao@mail.nih.gov:

3. Financial or Grants Management Contacts:

Jane Lin
Grants Management Branch
National Institute of Mental Health
6001 Executive Boulevard, Room 6154M, MSC 9605
Bethesda, MD 20892-9604
Telephone: (301) 443-3858
FAX: (301) 443-2229
Email: Linja2@mail.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:
Recipients of PHS support for activated involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf) as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm) as applicable.

Human Subjects Protection:
Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the

subjects and others, and the importance of the knowledge gained or to be gained (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm).

Sharing Research Data:
Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible (http://grants.nih.gov/grants/policy/data_sharing).

Investigators should seek guidance from their institutions, on issues related to institutional policies and local IRB rules, as well as local, State and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:
NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal, beginning with the October 1, 2004 receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Required Education on the Protection of Human Subject Participants:
NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

Human Embryonic Stem Cells (hESC):
Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (http://escr.nih.gov/). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

Public Access to Research Data through the Freedom of Information Act:
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:
The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule", on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs in NIH Grant Applications or Appendices:
All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review

because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Authority and Regulations:
This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Loan Repayment Programs:
NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The LRP is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40 hour week) for two years to the research. For further information, please see: http://www.lrp.nih.gov/.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Department of Health and Human Services

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892